Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics

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Key Words

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Abstract

Growth and development can be investigated using readily observable demographic factors such as weight and age. Size is the primary covariate and can be referenced to a 70-kg person with allometry using a coefficient of 0.75 for clearance and 1 for volume. The use of these coefficients is supported by fractal geometric concepts and observations from diverse areas in biology. Fat free mass (FFM) might be expected to do better than total body weight when there are wide variations in fat affecting body composition. Clearance pathways develop in the fetus before birth. The use of postnatal age as a descriptor of maturation is unsatisfactory because birth may occur prematurely; therefore postmenstrual age is a superior predictor of elimination function. A sigmoid E_{max} model (Hill equation) describes gradual maturation of clearance in early life leading to a mature adult clearance achieved at a later age.

1. INTRODUCTION

"The only principle of drug dosage which survives is that the dose must be adjusted to the individual patient" (1).

BSA: body surface area

CLcr: creatinine clearance

Growth and development are two major aspects of children not readily apparent in adults. These features can be investigated using demographic factors such as weight and age. How these factors interact is not necessarily easy to determine from observations because they exhibit colinearity. Drug elimination clearance, for example, may increase with weight, height, age, body surface area (BSA), and creatinine clearance (CLcr). All of these covariates may show a high degree of correlation and they are not mutually exclusive (2). Any one factor may or may not predict between subject differences in clearance.

Size models play a significant role in determining pediatric pharmacokinetic parameter estimates and consequently drug doses for young children, but it is important to appreciate their limitations. This review examines models used to describe the relationships between size, age, and pharmacokinetic parameters in children who range from premature neonates to young adults.

2. NORMALIZATION OF DOSE IN CHILDREN

Size is a common covariate used to determine dose in children. The normal variation of weight with age (from third to ninety-seventh percentile) is considerable, being least at 1 year (+25% to –20% at 10 kg) and reaching a maximum at approximately 13 years (+45% to –26% at 40 kg) (3).

Linear predictions of dose based on weight (per kilogram model) are used commonly, although it is now more widely recognized that there is a nonlinear relationship between weight and drug elimination. In 1940, Dawson (1) reviewed evidence that smaller species are generally more tolerant of drug treatment than larger species and concluded that doses increased less rapidly than predicted directly from weight. BSA was subsequently proposed in 1950 to be a more satisfactory index of drug requirements than body weight or age, particularly during infancy and childhood (4). Empirical drug dosage rules for children, based on BSA, have been proposed that use a percentage of an adult dose to calculate an appropriate child's dose (3, 5).

A size model using an exponent of weight has also been proposed (6) for scaling drug elimination clearance. The latter, which may be termed the allometric 3/4 power model has been found useful in normalizing a large number of physiological (7) and pharmacokinetic variables (8, 9).

The linear per kilogram, surface area, and allometric 3/4 power models are alternative approaches that have been described as a means of predicting physiological function from body size and thus to predict doses in children from adult values.

3. SIZE MODELS

We use the term size to refer to a transformation of observable factors, such as weight and height, that renders between-subject differences directly proportional to size.

For example if a linear model (the per kilogram model) is used to predict size, then size is the slope of the line (passing through zero when weight is zero) relating the dependent variable (e.g., clearance) to weight.

3.1. The Allometric Model

Most body size relations take the form

$$Y = a \cdot W^b, \qquad 1.$$

where Y is the biological characteristic to be predicted, W is the body mass, and a and b are empirically derived constants. Power relations like Equation 1 have been used to describe size relations in such diverse fields as paleontology (10, 11), animal morphology (12, 13), physiology (14, 15), ecology (16), and animal behavior (7, 17). Peters (7) has demonstrated that this simple relationship is a robust and powerful scientific theory when applied to the ecological implications of body size. These theories are realistic because they are built empirically using actual observations. They lend themselves to testing because they are quantitative (7).

In all species studied, including humans, the log of basal metabolic rate (BMR) plotted against the log of body weight (**Figure 1**) produces a straight line with a slope of 3/4 (7, 18–20). This log-linear function has the same slope in homeotherms, poikilotherms, and unicellular organisms (7). Mass- and temperature-compensated resting metabolic rates of microbes, ectotherms, endotherms (including those in hibernation), and plants in temperatures ranging from 0°C to 40°C are similar (21–23).

Explanations for this phenomenon vary. Kleiber (24) considered explanations that are based on changes in body composition with size. He concluded that the concentration of "active protoplasm" declines with size. This argument is supported by the finding that smaller species have higher concentrations of RNA, respiratory coenzyme, and enzymes (active protoplasm) per cell. These concentrations rise by a 3/4

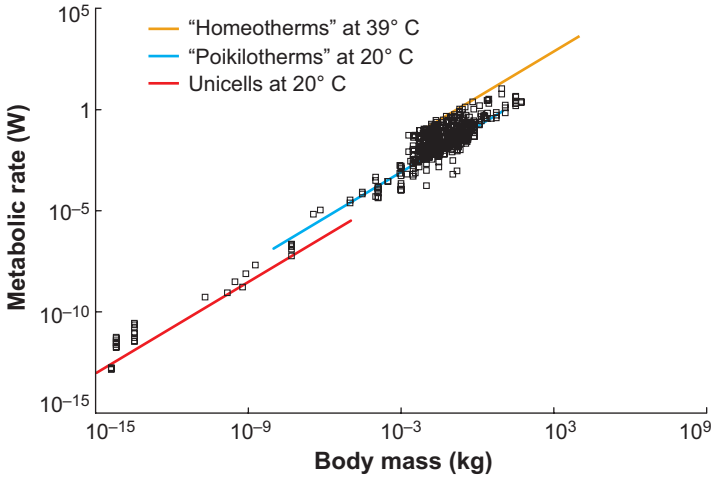


Figure 1

A comparison of the temperature-standardized relation for whole-organism metabolic rate as a function of body mass. The allometric 3/4 power model fits for unicells, poikilotherms, and homeotherms, uncorrected for temperature, are also shown. Adapted from Reference 21, with permission.

power function of weight ($W^{3/4}$) in each case (7, 25, 26). McMahon (27, 28) offers a structural explanation. Animals cannot remain isometric with increasing size, as loads would increase more than the ability of the skeleton to withstand such loads. Consequently, animals become stockier as size increases. The cross-sectional area of an animal's girth (and generally its limb muscles) increases as a 3/4 power function of weight. The maximum power a muscle can produce depends on cross-sectional area. If the metabolic rate of an organism is proportional to power production of its muscles, then metabolic rate rises with muscle cross-sectional area and $W^{3/4}$.

West et al. (29, 30) have used fractal geometric concepts to explain this phenomenon. This group analyzed organisms in terms of the geometry and physics of a network of linear tubes required to transport resources and wastes through the body. Such a system, they reasoned, must have three key attributes: The network must reach all parts of a three-dimensional body; a minimum amount of energy should be required to transport the materials in a fluid medium; and the terminal branches of the networks should all be the same size, as cells in most species are roughly similar sizes. The 3/4 power law for metabolic rates was derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes. These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms (23, 30, 31). Values of allometric exponents for variables of the mammalian cardiovascular and respiratory system predicted by the allometric model compared with empirical observations are shown in **Table 1**. While there is substantial empirical evidence for the 3/4 power allometric model there still remains controversy about its general applicability (32). For example, the allometric coefficient may be less than 3/4 when clearance is through

Table 1 Values of allometric exponents for variables of the mammalian cardiovascular and respiratory system predicted by the allometric model compared with empirical observations

Variable	Predicted	Observed
Blood volume	1	1
Tidal volume	1	1.041
Skeletal mass	1	1.08
Cardiac stroke volume	1	1.03
Lung volume	1	1.05
Cardiac output	0.75	0.74
Metabolic rate	0.75	0.75
Volume flow to lung	0.75	0.8
Total lung resistance	–0.75	–0.7
0_2 consumption rate	0.75	0.76
Glucose turnover	0.75	0.75
Circulation time	0.25	0.25
Cardiac frequency	–0.25	–0.25
Respiratory frequency	–0.25	–0.26

Data taken from West et al. (30).

Table 2 Key references detailing the development of the allometric 3/4 power model

Year	Event	Reference
1637	Galileo discussed relationship of skeletal size to body mass	(8, 143)
1839	Sarrus & Rameaux propose "surface law" to French Royal Academy	
1932–1934	Brody & Kleiber establish that log (BMR) plotted against the log(body weight) produces a straight line with a slope of 3/4	(18, 19)
1931–1937	Brody & Carrel define physiological time	(144, 145)
1949	Adolph relates physiological properties in various animals to body weight	(35)
1961	Kleiber considers explanations that are based on changes in body composition with size	(24)
1970	Application of physiological time onto plasma time-concentration profiles from different species	(39)
1973	McMahon offers a structural explanation	(27)
1977	Introduction of allometric equations in pharmacokinetic parameter scaling	(146)
1983	Peters considers the ecological implications of body size	(7)
1984–1995	Comprehensive reviews about the role of allometry in pharmacokinetics	(8, 42, 147–149)
1997+	Fractal geometry to mathematically explain this allometric 3/4 power model.	(21, 23, 26, 29–31)

Extended from Boxenbaum (8).

renal elimination (33). A historical overview of the development of the allometric power models is shown in **Table 2**.

This allometric power model may be used to scale metabolic processes such as drug CL as follows:

$$CL_i = CL_{std} \cdot \left(\frac{W_i}{W_{std}}\right)^{3/4}, \qquad 2.$$

where CL_i is the clearance in the individual of weight W_i and CL_{std} is the clearance in a standardized individual with weight W_{std} (6).

An example clearly showing the curvilinear relationship between weight and CL is shown in **Figure 2**. The authors of this study estimated the allometric coefficient for

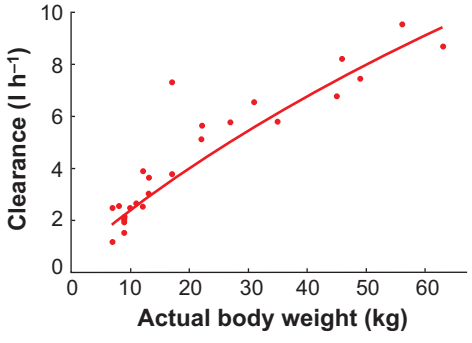


Figure 2

Allometric curvature observed in busulphan clearance. From Reference 45, with permission.

Table 3 Examples that support the proposal that CL scales allometrically within humans

Drug	N	Age	Weight (kg)	Allometric coefficient	95% confidence interval	CV	Reference
Propofol	270	2–88 years	Range 12–100	0.76			(66)
Propofol	22	3–17 months	Range 8.3–12.5	0.61	0.38, 0.84	19.7%	(150)
Busulfan	24	3 months–16 years	Mean 23.8 Range 7.1–62.6	0.74	0.59, 0.90	10.7%	(45)
Phenytoin	322	18.4 SD 17.3 years 3 data sets (*a*) 29.5 SD 15.2 years (*b*) 6.05 SD 3.95 years (*c*) 1.33 SD 0.62 years	(*a*) 54.4 SD 16.7 (*b*) 22.9 SD 11.6 (*c*) 11.8 SD 2.07	0.63	0.58, 0.67	3.7%	(63)
Oxycodone	39	6 months–7 years	Mean 16.3 Range 8–43	0.87	0.64, 1.10	13.3%	(151)
Pyrimethamine	89	1 week–14 years	Range 3–59	0.53	0.47, 0.59	5.8%	(34)
Sulfadoxine	89	1 week–14 years	Range 3–59	0.64	0.58, 0.70	4.8%	(34)
Methotrexate	49	6 months–17 years	Mean 30.56 Range 7.46–80	0.88			(152)
Valproate	225	0.1–14 years	Mean 31.3 Range 4–74	0.72	0.66, 0.77	4.2%	(153)
Sotolol	76	0.03–17 years	Mean 16 (SD 17.1)	0.58	0.42, 0.74	14.4%	(154)

Ninety-five percent confidence interval assuming normal distribution of estimation error. CV taken from original source or calculated from reported standard error or confidence interval.

CL with a value of 0.742, which is practically indistinguishable from the theoretical value of 0.75.

Other examples of CL scaling allometrically within humans are shown in **Table 3**. The allometric exponent ranges from 0.53 to 0.88 in these examples. The model used to describe maturation clearance changes with age will have an influence on the allometric exponent estimation. The low exponents estimated for pyrimethamine and sulfadoxine (34) may be attributable to a failure to account for clearance maturation with age. There are some examples of allometric coefficients whose confidence interval does not include the expected value of 0.75. In all such cases, the reported coefficient of variation of the estimate seems unrealistically small compared with expected values, shown in **Table 4**.

When applied to physiological volumes (V), the power parameter is 1:

$$V_i = V_{std} \cdot \left(\frac{W_i}{W_{std}} \right)^1 . \qquad 3.$$

This index has been demonstrated for blood volume, vital capacity, and tidal volume (20, 29, 35–37). The volume of distribution of the central compartment (V_c), the volume of distribution by area (V_{beta}), and the volume of distribution at steady state (V_{dss}) also show direct proportionality to body weight (38).

Time-related indices (T), such as heart rate, respiratory rate, or drug half-times have a power of 1/4 (7, 9, 23, 28, 29, 39, 40):

$$T_i = T_{std} \cdot \left(\frac{W_i}{W_{std}}\right)^{1/4}. \quad 4.$$

The pharmacokinetic time scale originated from the concept of physiologic time. Most mammalian species have the same number of heartbeats and breaths in their life span. The difference between small and large animals is that smaller animals have faster physiologic processes and consequently a shorter life span (9). This power function of 1/4 can also be derived mathematically for pharmacokinetic half-times based on more sound allometric theory:

$$T_{1/2} = \ln(2) \cdot \frac{V}{CL} \alpha \ln(2) \cdot \frac{W^1}{W^{3/4}} = \ln(2) \cdot W^{1/4}. \quad 5.$$

The allometric power family of models allows comparison of pediatric parameter estimates with adult estimates. We might anticipate that clearance is reduced in neonates compared with adults because of immaturity of elimination pathways. This reduction in neonatal clearance may not be apparent when clearance is expressed using the linear per kilogram model. For example, if a clearance of 0.2 L h^{-1} kg^{-1} is estimated in both adult (70 kg) and neonate (4 kg), we might incorrectly assume clearance is mature at birth. When these values are standardized to a 70 kg person using an allometric 3/4 power model (Equation 2), then clearance in the adult is 14 L h^{-1} 70 kg^{-1} and clearance in the neonate 6.9 L h^{-1} 70 kg^{-1}. Neonatal clearance is reduced compared with adult.

3.2. The Surface Area Model

The original surface area model proposed by Du Bois & Du Bois (41) was predicted from nine adults of diverse body shape. These nine individuals included a tall thin adult male, a fat adult woman, and a 36-year-old cretin with the "physical development of a boy of 8 years." The youngest individual from this group was 12 years old. It is now common practice to use the Du Bois & Du Bois formula (41) to predict surface area from weight (W) and height (H):

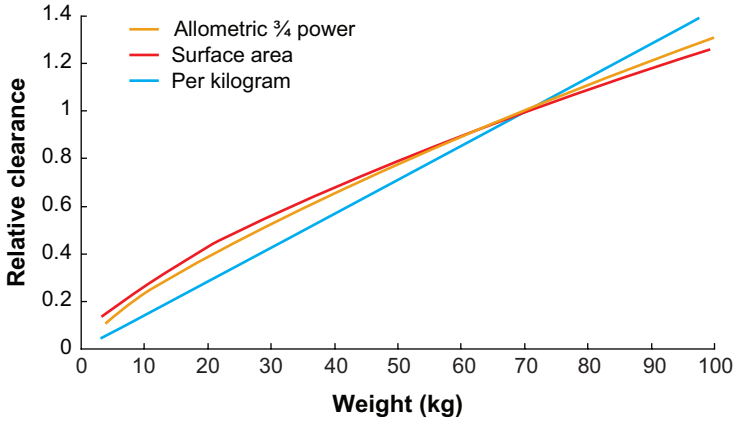
$$BSA = W(kg)^{0.425} \cdot H(cm)^{0.725} \cdot 0.007184. \quad 6.$$

This formula belongs to the same class of allometric models that includes those using weight alone.

Nomograms determined from this formula are often used. Surface area can also be estimated from an allometric model with a power parameter of 2/3 (6, 42). This allometric 2/3 power model assumes metabolic rate is scaled by geometric descriptors of body size (43). The surface area formula assumes that adults and children are geometrically similar. However, infants are not morphologically similar to adults—infants have short stumpy legs, relatively big heads, and large body trunks. The accuracy of the surface area formula in children is doubted (44). Precision of the Du Bois & Du Bois formula has been confirmed in adults in whom BSA was measured

Figure 3

Relative clearance changes with weight for the three models over the human weight range. A 70-kg person has a normalized clearance of 1 for each model. From References 6 and 46, with permission.



by direct photometric measurement (44), but underestimation anticipated when a predicted surface area of less than 1.3 m^2 is present (an average 12-year-old child).

When a standard surface area of 1.9 m^2 is used with the allometric 2/3 power surface area model, clearances agree quite well with the 3/4 power model except at body weights below 7 kg. If a standard surface area of 1.73 m^2 is used, this method consistently overpredicts by 10%. When the allometric surface area is used, clearance is over predicted by more than 10% at body weights below 20 kg (**Figures 3** and **4**) (6).

The allometric surface area model does not fit known observations in mammals (24, 29, 30). The body area of animals rises more slowly than the surface law would suggest, as larger animals are stockier. The surface area model refers to an animal's skin area. Surfaces used in energy exchange, such as gut villi or respiratory alveoli, bear a distant relation to this external skin surface. The mass of empirical evidence suggests that the appropriate scaling factor is significantly different from 0.67 and is actually 0.75 (26, 47, 48). Nevertheless, the surface law continues to be widely used, particularly with drugs that have a low therapeutic index, such as those used in oncology.

When CL is calculated using the allometric surface area model and compared with the 3/4 power model, the two models are in close agreement for the human weight range (**Figures 3** and **4**) above 20 kg. Divergence increases below 20 kg and above 120 kg. Despite this divergence at lower weights, the surface area model has been widely used to scale drug doses for children out of infancy.

3.3. The Linear Per Kilogram Model

The linear per kilogram model is the poorest model when used for interspecies scaling of metabolic processes such as total body clearance, but remains the most commonly used in humans. Clearance, expressed per kilogram of body weight, is larger in children than adults. Developmental and physiological changes during growth, such as an increased relative liver size or increased hepatic blood flow, have been invoked (49)

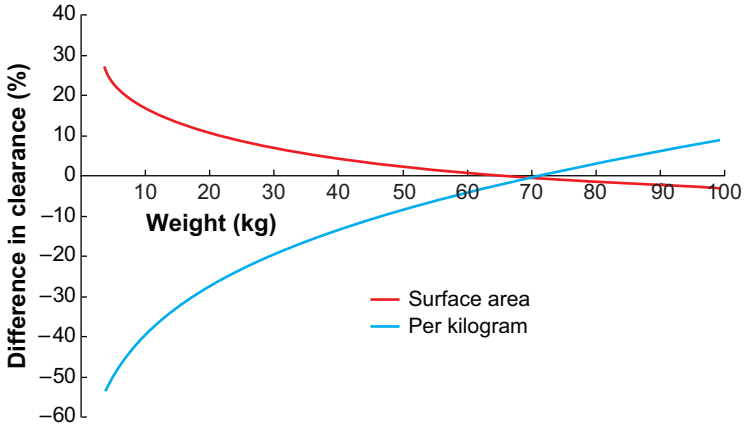


Figure 4

Percent differences in clearance determined by the surface area and per kilogram models when compared with the allometric 3/4 power model. From References 6 and 46, with permission.

to explain this higher clearance per kilogram. However, clearance is also increased for drugs that are eliminated by pathways other than those found in the liver or kidney. Remifentanil, a synthetic opioid cleared in part by plasma esterase, also has an apparently increased clearance in children (69.4 ml min^{-1} kg^{-1}) (50) relative to adults (34 ml min^{-1} kg^{-1}) when scaled per kilogram (51). These clearance estimates become similar when scaled allometrically (2450 ml min^{-1} 70 kg^{-1}).

In humans, prediction using adult clearance values and the per kilogram model leads to an underprediction of more than 10% at body weights less than 47 kg when compared with the allometric 3/4 power model. This discrepancy increases as size decreases and approaches 50% for a newborn human of 3.5 kg (**Figures 3** and **4**). Paradoxically, because clearance is reduced in this age group for developmental reasons, use of the linear per kilogram model may get close to the right answer for the wrong reason.

Figure 5 shows clearance changes with weight for a hypothetical drug using the three different models. Age-related clearance increases throughout infancy and reaches adult rates at approximately one year using an allometric 3/4 power model. The linear per kilogram model shows an increased clearance compared with adults at approximately one year (10 kg). This increased clearance in infants has been interpreted to mean that children have an enhanced capacity to metabolize drugs. It is more likely that the increased clearance seen in one-year-old children is an artifact owing to the per kilogram model.

3.4. Fixing or Estimating the Allometric Coefficient?

While the surface area model has proven unsuccessful for interspecies scaling (52), the allometric 3/4 power model has been used with success for cross-species scaling in pharmacokinetics (53–58), although correction factors are sometimes required to account for differing metabolic pathways (58–60). Within the human species, except for neonates and infants where maturation of clearance mechanisms is incomplete,

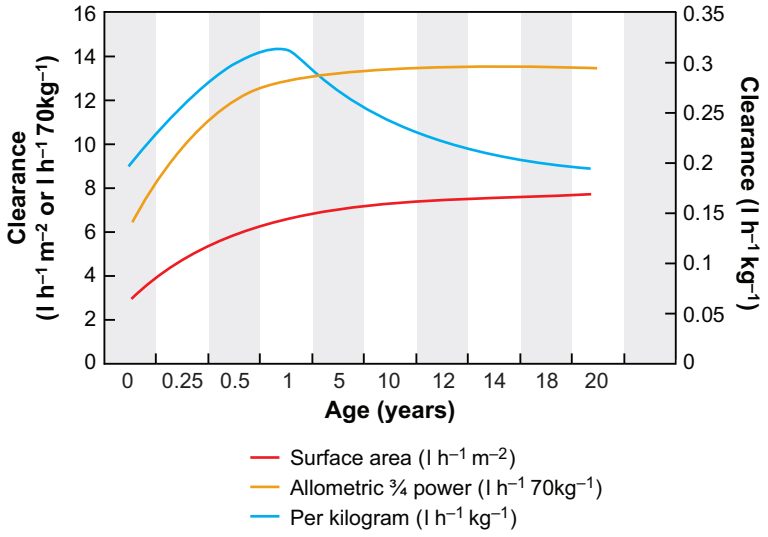


Figure 5

Age-related clearance changes for a hypothetical drug. All three models show an increase in clearance over the first year of life owing to maturation of metabolic pathways. Clearance expressed using the per kilogram model then decreases with age after 1 year to reach adult levels in adolescence. This course is not evident with the allometric 3/4 power and surface area models. From Reference 46, with permission.

the pharmacokinetics of many drugs in children can be predicted using weight and adult estimates.

Size models simplify population pharmacokinetic modeling in children. Children out of infancy can range in weight from 10 kg to 100 kg. The pharmacokinetics of acetaminophen (61, 62), phenytoin (63), theophylline (64), ibuprofen (65), propofol (66), and morphine (67) have been successfully modeled using allometric power models.

Allometric size parameters are often fixed (e.g., 0.75 for clearance, 1 for volumes of distribution) based on the established scientific framework described above. Investigation of acetaminophen (61), zidovudine (68), itraconazole (69), propofol (70), and ciprofloxacin (71) in children, for example, used fixed allometric coefficients. However, the allometric coefficient is sometimes estimated (45, 63, 66) in pharmacokinetic analyses.

It is perhaps not so well appreciated that estimates of the allometric coefficient may be quite imprecise depending very much on the distribution of weight in the subjects. Hu & Hayton investigated a wide number of studies that claimed to find allometric exponents different from 3/4 and concluded in almost all cases that the estimated value was indistinguishable from 3/4 (33). We performed a simulation experiment using a very simple pharmacokinetic study design. One concentration measurement was made per subject during a continuous infusion at steady state. This is an optimal design for estimating clearance. Clearance was assumed to be related to weight with an allometric coefficient of 0.75 and then randomly log normally distributed with an apparent coefficient of variation of 30%. The residual random error in the measurement of concentration was 10% of the true value. The effective random variability of the clearance estimate would be the sum of these two random effects, i.e., 31.6%. The distribution of randomly simulated clearances

Table 4 Imprecision of estimates of allometric coefficient for clearance (true value 0.75)

Weight distribution	5%CI	95%CI
Log normal median 70 kg, 20%CV	0.48	1.01
Log normal median 70 kg, 50%CV	0.64	0.86
Uniform 0–140 kg	0.69	0.81

Estimation was performed using NONMEM V 1.1 with the FOCE interaction method. Empirical confidence interval (CI) and CV (standard deviation/average) from parametric bootstrap distribution of 1000 replications. One hundred subjects were drawn from each weight distribution for each replication.

was truncated within the range of 0.1 times the mean up to 10 times the mean clearance.

Concentrations were simulated for 100 patients with three different distributions of weight. A relatively large clinical trial in a patient population may typically have 20% variability in W (72). The imprecision in the estimate of the allometric exponent had a CV of 22% with this kind of weight variability (**Table 4**). Much larger weight variability, e.g., log normal with 50% CV or a uniform distribution from 0 to 140 kg, would be very unlikely to occur in practice, but even with such extreme variability, the 90% interval of estimates does not include the first significant digit of the true value.

In real life, experimental designs for estimating clearance are much less robust and the error in estimation of the allometric coefficient can be expected to be larger than those shown in **Table 4**. We find it difficult to accept claims that are made that the allometric coefficient is different from 3/4 based on estimation from almost any realistic study design. The exponents 0.75, 0.80, and 0.85, for example, provided the same degree of accuracy or error in the prediction of clearance in children (73).

Conversely it is effectively impossible to prove that the allometric coefficient for clearance is 3/4 based on experimental data. We are not aware of any consistently replicable estimates of allometric coefficients that are significantly different from 3/4, and thus we do not accept that there is evidence to reject allometric theory for predictions of drug clearance in humans.

In the absence of any strong evidence to reject allometric theory, we believe there is nothing to lose and several things to gain by accepting the allometric scaling model as a consistent and biologically plausible predictor of how clearance varies with weight. The most obvious application of assuming the allometric theoretical model is in separating out the separate effects of growth (weight) and maturation (age) on pharmacokinetic parameters.

3.5. Practical Simplifications of Size Models for Clinical Use

The therapeutic ratio for most drugs is more than 50% (3), so some dose approximation can often be made with safety. This safety net has resulted in the promulgation of formulas that "simplify" the allometric calculation (e.g., using surface area) of drug dosage in children. For example "less than 30 kg, a child's drug dose may be

NONMEM: a nonlinear mixed effects modeling program

Table 5 Pediatric maintenance doses of drugs expressed as a percentage of adult dose using an allometric 3/4 power model. The neonatal estimate based on size has been reduced further by 50% to account for age-related maturational changes of clearance

Approximate age	Weight (kg)	Percentage of adult dose	Fraction of adult dose
Birth	3.2	5	1/20
2 months	4.5	13	1/8
4 months	6.5	17	
12 months	10	23	1/4
18 months	11	25	
5 years	18	36	
7 years	23	43.5	
10 years	30	53	1/2
11 years	36	61	
12 years	40	66	
14 years	45	72	3/4
16 years	54	82	
Adult	70	100	1

From Reference 155.

(W × 2)% of an adult dose; over 30 kg, (W + 30)% of an adult dose" (3). Even simpler, the reference points at which the dose is 1/8, 1/4, 1/2, and 3/4 of the adult dose can be memorized as approximately 1 month, 1 year, 7 years, and 12 years, respectively, as proposed for drugs used in anesthesia (74).

Maintenance dosing is determined by clearance. Consequently, it is possible to predict the maintenance dose for children by scaling the adult dose using allometry (**Table 5**). A factor for immaturity has been included for the values for neonates shown in **Table 5**, but clearance pathways mature at different rates and some pathways (e.g., N-acetyltransferase) may not mature until 4 years of age (75). In some cases, stage of development can alter the action of, and response to, a drug—a truly age-dependent difference in pharmacodynamics (76). This may be true of both the desired action [e.g., warfarin (77), ciclosporin (78)] and adverse events [stilbestrol (79)]. Well-conducted PKPD or PK studies are still needed to determine the most appropriate doses for neonates, infants, children, and adolescents (80).

4. MATURATION OF CLEARANCE

4.1. Age

Maturation of pharmacokinetic parameters is usually expressed using age as the primary covariate. These developmental aspects have been investigated using two broad approaches.

4.1.1. Physiologically based pharmacokinetic modeling. Organ maturation, body composition, and ontogeny of drug elimination pathways have marked effects on

pharmacokinetic parameters in the first few years of life. PBPK models require detailed physiological data. Data on ontogeny of individual clearance pathways, derived from measurements of enzyme expression and activity in postmortem livers (81, 82) and from in vivo data from drugs that are cleared by similar pathways are useful (80). Continued input of information concerning genetic, physiological, organ and tissue size and composition, protein binding, and demographic and clinical data into the library and algorithms for PBPK modeling programs have progressively improved PBPK model prediction ability (80, 83–96). These models have been used to assist with first-time dosing in children (83–86, 97). A general PBPK model for drug disposition in infants and children, covering the age range from birth to adulthood, has been successfully evaluated using theophylline and midazolam as model drugs (91). The introduction of population variability in enzyme abundance and activity, for example, contributes to between-individual variability estimates.

PMA: postmenstrual age
PNA: postnatal age

4.1.2. Mathematical functions relating age to clearance maturation. Holford (6) stresses that the use of size as the first covariate when attempting to explain differences between individuals offers a systemic approach to disentangle competing covariate influences. Once size is standardized, the effects of other covariates such as age (61), temperature (98, 99), and renal function (67) can be investigated within a given data set describing time-concentration profiles in a population. Age is used to describe maturation of clearance. The quantitative models used to describe this maturation process vary depending on the span of the ages under investigation. A linear model is commonly used for a population sample limited to a small defined age band. An exponential model may describe the gradual increase of clearance in premature neonates (100), whereas an asymptotic exponential process has been used to describe clearance maturation from birth to adolescence (61).

Maturation of clearance begins before birth, suggesting that postmenstrual age (PMA) would be a better predictor of drug elimination than postnatal age (PNA). The fetus is capable of metabolizing morphine (hepatic enzyme uridine 5′-diphosphate glucuronosyl transferase-2B7, UGT2B7) from 15 weeks gestation (101, 102). The neonate can use sulfate conjugation as an alternative route for substrates such as morphine or acetaminophen before glucuronidation matures. There are distinct patterns associated with isoform-specific developmental expression of the cytochrome P450 (CYP) enzymes. CYP2D6 has been detected in premature neonates as young as 25 weeks PMA (103). Although some CYPs appear to be switched on by birth, whereas in others birth is necessary but not sufficient for the onset of expression (81, 104, 105), there are no direct demonstrations that clearance changes as a consequence of being born. Maturation of clearance in neonates may be described by both PMA and PNA, but PMA is a more physiologically appropriate covariate to explain the time course of changes in clearance.

An example of a linear model investigating age-related changes for clearance is

$$F_{PME} = 1 + SLPCL \times (PMA - 40), \qquad 7.$$

where F_{PMA} is the factor for PMA and is centered on 40 weeks PMA (full-term gestation), PMA is the postmenstrual age in weeks; *SLPCL* is a parameter describing changes of clearance with PMA.

βcl: a parameter estimating the fractional CL_{std} at a specified PMA

MATCL$_{50}$: the PMA at which clearance is 50% that of the mature value

Alternative models (exponential, asymptotic exponential, sigmoid E_{max}) can approximate the linear model over a narrow age range (e.g., premature neonates). Maturation of clearance begins developing before birth and extrapolation of a linear function does not allow this. An exponential function allows for a gradual increase in clearance at earlier PMAs. This exponential function was used by Kimura et al. in their study of vancomycin pharmacokinetics in neonates (106):

$$F_{PME} = EXP\left(SLPCL \times (PMA - 40)\right). \qquad 8.$$

An exponential model may be a more robust empirical model than the linear model because the prediction is always positive. However, this exponential function, in common with the linear model, extrapolates badly by predicting continuously increasing clearance with age. Parameters estimated in neonates and children lead to unrealistic prediction of adult clearance because clearance is known to approach a plateau at some age (and may decline in the elderly even after adjustment for size and renal function). An exponential asymptotic model, similar to models based on first-order processes that are common in biological systems, has been previously used to investigate clearance maturation of other drugs during infancy (61, 67). A "mature" or "adult equivalent" clearance can be estimated at a plateau:

$$F_{PMA} = (1 - (1 - \beta cl)) \times EXP\left(-(PMA - 40) \times \frac{Ln\,(2)}{Tcl}\right), \qquad 9.$$

where *βcl* is parameter estimating the fractional CLstd at 40 weeks PMA and *Tcl* describes the maturation half-life of the age-related changes of clearance. This model has been used to investigate acetaminophen (107) and morphine (67) age-related clearance maturation, suggesting maturation half-lives of these glucuronide-dominant clearance systems to be 3–4 months.

This asymptotic exponential model extrapolates poorly because it predicts zero clearance at a time when gestation is well advanced and the liver and kidneys are expected to be functional. A sigmoid E_{max} model allows gradual maturation of clearance in early life and a "mature" clearance to be achieved at a later age (**Figure 6**):

$$F_{PMA} = \frac{PMA^{HillCL}}{PMA^{HillCL} + MATCL_{50}^{HillCL}}, \qquad 10.$$

where *MATCL*$_{50}$ is the PMA at which clearance is 50% that of the mature value and *HillCL* is the Hill coefficient for clearance. A sigmoid E_{max} model has been used to investigate vancomycin clearance and covariate effects in premature neonates (108). The use of a sigmoid E_{max} model to describe the relationship between clearance and PMA predicted a reasonable adult clearance of 3.79 (95%CI 2.76–4.98) liters h^{-1} 70 kg^{-1} from premature neonatal data (108). Scaling adult data to predict infant clearance is unreliable in infancy because the rate and extent of maturation is unknown. On the other hand scaling neonatal data may predict adult clearance when size and age are included as covariates.

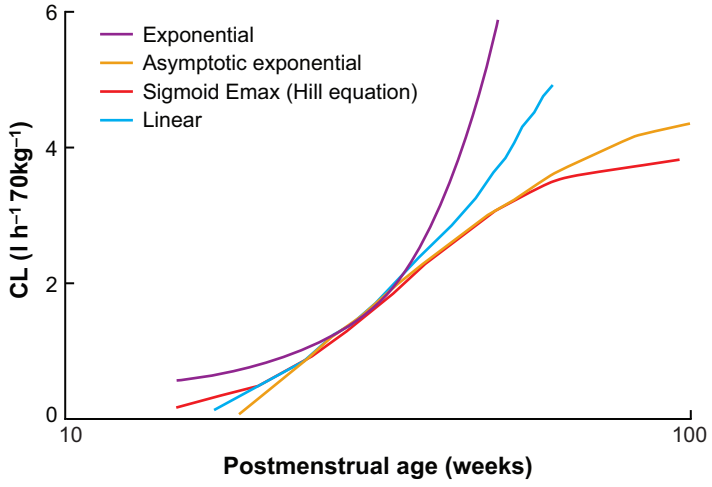


Figure 6

Clearance estimates are similar for all models (exponential, asymptotic exponential sigmoid E_{max}, linear) over the narrow age band (24–36 weeks PCA). The linear and asymptotic exponential models suffer because they assume zero clearance at times long after gestation and organ maturation have started. The exponential model predicts unrealistic values in adults. A sigmoid E_{max} model allows for gradual maturation of clearance in early life and a mature clearance to be achieved at a later age. From Reference 109, with permission.

Plasma esterases are responsible for the hydrolysis of propacetamol to paracetamol. The half-life of formation of paracetamol by hydrolysis has been investigated (62). The half-life was the same in all age groups when standardized for size (46), but it was faster in the younger patients. Remifentanil is also cleared by plasma esterases and its clearance is similarly fastest in the newborn period when expressed on a per kilogram basis (50, 51, 110–112).

These models for the effect of age on clearance may prove useful in teasing out information concerning possible temporal switches that "turn up" clearance at birth. It is postulated that birth may have an effect on ontogeny of clearance. The disappearance of the placenta as an external clearance organ may also play a role. The placenta has enzyme capacity to clear drugs (e.g., CYP P450 and conjugation) and interpretation of hepatic maturation remains unknown in the fetus.

4.2. Renal Function

The clearance maturation of drugs that are extensively cleared by renal elimination is a reflection of the time course of development of glomerular filtration rate (GFR). Estimates for amikacin clearance (100) mirror GFR estimates in premature neonates (113, 114). GFR matures during infancy and approaches an adult rate (6 liters h^{-1} 70 kg^{-1}) by 6 months PNA (115, 116). Difficulties arise determining renal function in children, although a number of formulas have been published that allow estimation of GFR from clinical characteristics (117). These formulas use simple markers such as

height, creatinine concentration in plasma, and BSA. Estimation of GFR is acceptable in adults, but prediction is poor in children with a GFR value less than 40 ml min^{-1} (118).

CPR: creatinine production rate

Creatinine concentration decreases with age in the newborn. Consequently, vancomycin clearance estimates have been made using an inverse relationship to creatinine concentration in premature neonates (119). Creatinine concentration in the first few days of life reflects maternal concentrations more than neonatal renal function, and subsequent concentrations are influenced by tubular reabsorption (120). Attempts to use the Cockcroft & Gault models (121) to predict creatinine production rate (CPR) fail. CLcr can be predicted after these first few days of life using PMA as a covariate to predict CPR with a scaling constant ($K_{age} = 0.00823$) for age (108). This is based on assuming a CPR of 516 μmol h^{-1} in a 70 kg, 40-year-old male (121):

$$CPR = 516 \times EXP\left(0.00823 \times \left(\frac{PMA(wk) - 40}{52} - 40\right)\right) \times \left(\frac{W(kg)}{70}\right)^{3/4} \ \mu\text{mol}\,\text{h}^{-1} \quad 11.$$

The increase of CPR with age in neonates is assumed to be a consequence of increasing muscle bulk with age as opposed to the decrease in muscle bulk that occurs with age in adults.

A population modeling approach has been used to directly estimate GFR in children 0.8–18 years old with renal disease. The use of squared length compensates for the nonlinear relationship between muscle mass and age-related changes of serum creatinine (122):

$$CPR = 0.945 \times W(kg) + 0.00237 \times Length\,(cm)^2 \ \mu\text{mol}\,\text{h}^{-1}. \quad 12.$$

The CPR predicted from either Equation 11 or Equation 12 can be used with a measured serum creatinine (Scr) to predict CLcr with Equation 13:

$$CLcr = \frac{CPR}{\text{Scr}\ \mu\text{mol/L}}\ \text{L}\,\text{h}^{-1} \quad 13.$$

Cole et al. (118) also used a population approach to investigate CLcr in 50 pediatric cancer patients of similar age range (0.8–19.8 years) and reported an empirical linear model:

$$CLcr = 2.21 + 0.115 \times W - 0.0282 \times Scr\ \text{L}\,\text{h}^{-1} \quad 14.$$

Note that this model should be used with caution because it can predict negative creatinine clearances e.g. weight of 14 kg and Scr 140 μmol L^{-1}.

Nephrogenesis starts in the embryo at approximately week 5 and nephrons become functional by week 8. Nephrogenesis is complete at gestational week 36 when there are approximately 1,000,000 nephrons in each kidney. The kidneys are anatomically and functionally immature at birth. GFR is reported to double by one week of age (123). Maturation in the first few months of life has been described as an exponential process (124, 125). Although it has been claimed that preterm infants had a slower increase in GFR during their first weeks of life (126) compared with full-term infants, the lack of repeated measurements in the same child makes it impossible to distinguish changes owing to maturation from those associated with birth.

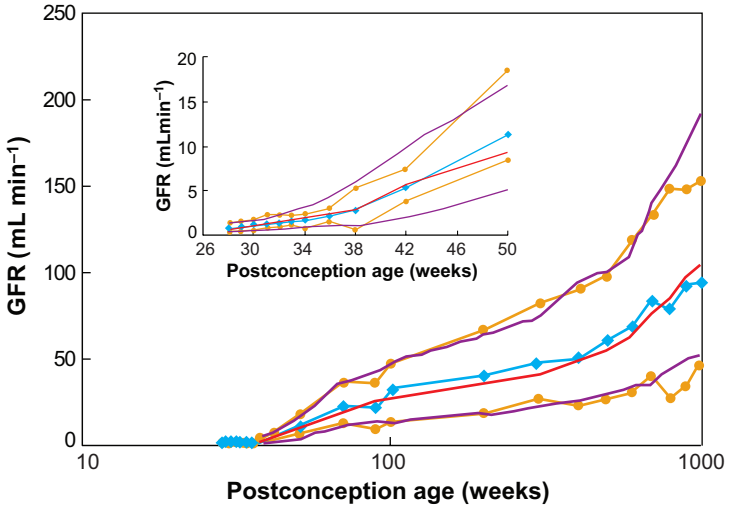


Figure 7

An allometric size and sigmoid E_{max} postmenstrual age model adequately described maturation of measured GFR in children who ranged from premature neonates (28 weeks PMA) to young adults (18 years old). Measured GFR (inulin, ^{51}Cr-EDTA, Tc^{99m}-DTPA or iohexol) observations fit between the 95% confidence intervals predicted by the model. The blue line and red line are the median and 90% prediction intervals for the combined age and size models. The yellow and purple lines are the median and 90% intervals for observed GFR.

We have used an allometric 3/4 power model and sigmoid E_{max} maturation model based on PMA to describe GFR in a population including premature and full-term neonates, infants, children, and young adults (**Figure 7**). This model predicts GFR as a function of PMA and weight. If an independent measure of GFR is available, e.g., Equation 13, then renal function can be calculated as a fraction of the predicted normal value.

5. MATURATION OF VOLUME OF DISTRIBUTION

Total body water constitutes 85% of the body weight in the preterm neonate and 75% in full-term neonates. This decreases to approximately 60% at 5 months and remains relatively constant from this age forward. The major component contributing to this reduction in body water is the decrease in ECF. ECF constitutes 45% of the body weight at birth and 26% at 1 year. There is a further ECF reduction during childhood until adulthood, where it contributes 18% (127). The percentage of body weight contributed by fat is 3% in a 1.5-kg premature neonate and 12% in a full-term neonate; this proportion doubles by 4–5 months of age. "Baby fat" is lost when the infant starts walking and protein mass increases (20% term neonate, 50% adult) (128). Albumin, globulin, lipoprotein, and glycoprotein concentrations change over the first year affecting drug binding (129). Relative body proportions change dramatically over the first few years of life and may affect volumes of distribution of drugs.

ECF: extracellular fluid

FFM: fat free mass

Volume of distribution changes and their relation to age, which occur as a consequence of body composition changes, can be described using quantitative functions similar to those used for clearance maturation. Equation 9 has been used to describe morphine and paracetamol volume of distribution changes with age. Morphine volume of distribution is reduced in neonates and increases with a maturation half-life of 26 days from 83 L 70 kg g^{-1} at birth (67). Paracetamol (acetaminophen) volume of distribution decreased exponentially with a half-life of 1.9 days from 120 L 70 kg^{-1} at birth to 69.9 L 70 kg^{-1} by 14 days (107). BSA has been claimed to be linearly related to extra-cellular fluid (ECF) volume in neonates and infants (130). The volumes of distribution for neuromuscular blocking drugs in this age group closely approximate ECF and BSA is a common standardization for initial dosing (131). This is unexpected because volumes are associated with a weight exponent of 1, not 2/3. However, the original data that related ECF to size (130) were noted to have a nonlinear relationship to weight and the surface area model was the only alternative model to the per kilogram model that was tested. No account was taken of changes in ECF that might be related to age, which could explain changes in ECF that were not related linearly to changes in weight.

6. MATURATION OF HALF-LIFE

Half-life is a secondary parameter, derived from clearance and the volume of distribution. Independent maturation changes in these two parameters will affect half-life estimation. Reports that refer to the change in half-life of a drug with age in children can be misleading because of independent changes of volume of distribution and clearance with growth and development.

Polar drugs, such as aminoglycosides and neuromuscular blocking drugs (NMBD), distribute rapidly into the ECF, but enter cells more slowly. The initial dose of these drugs, expressed as milligrams/kilograms, is usually higher in the infant compared with older children and adults because of an increased ECF volume in infants. Although we predict volumes to have a linear relationship to weight, ECF is nonlinearly related to weight, possibly as a consequence of age-related factors pertaining to water turnover rate. If doses are expressed using a surface area model or allometric 3/4 power model, there is no difference in doses producing equivalent effect (131, 132). Understanding these relationships is complicated by unknown pharmacodynamics and the need to consider differences in the rate of distribution of drugs to their site of action.

Dose at different ages, however, is dependent on the complex interweaving of pharmacodynamic as well as pharmacokinetic factors. Fisher et al. have unraveled some of these aspects for d-tubocurarine (131) in children. The allometric model predicts a linear relationship with weight, but the volume of distribution mirrors ECF changes and can be predicted with an allometric 3/4 power model. This is because ECF is a major contributor to the volume of distribution. Allometric volume prediction is altered by age-related development. Clearance, standardized to an allometric or surface area model, is reduced in neonates and infants compared with older children and adults. These age-related clearances resemble age-related changes in glomerular filtration. These independent clearance and volume changes in early life have impact on reported distribution half-lives of NMBDs (46).

7. BODY COMPOSITION

The allometric models use weight as a descriptor of body size. Other size descriptors include ideal body weight, lean body mass, fat free mass (FFM), body cell mass, or liver weight (133–139). The size descriptor that perhaps is closest to capturing the concept of body weight that is used in allometric theory is FFM. Allometric theory for homeotherms is developed primarily on the basis of connecting structure to function (29). Fat is a structural feature of the body that contributes little to the metabolic rate and thus FFM might be expected to do better than total body weight when there are wide variations in fat affecting body composition.

NFWT: normal fat weight

Prediction equations for FFM have been developed based on a semimechanistic theory (133). This semimechanistic model can be compared with that used for predicting renal function using the Cockcroft & Gault method (121). FFM is predicted using observed total weight (TWT), height (H), and sex (144):

$$FFM = \frac{WHS\max \cdot H^2 \cdot TWT}{Ht^2 \cdot WHS_{50} + TWT}$$
$$NFWT = FFM + FFAT \cdot (TWT - FFM). \qquad 15.$$

WHSmax is 42.92 and WHS_{50} is 30.93 in men and 37.99 and 35.98, respectively, in women. Extra fat weight is obtained from the difference between TWT and FFM. The sum of FFM and extra fat weight can be used to predict normal fat weight (NFWT). The fat weight fraction, FFAT, reflects the contribution of fat to the apparent weight of the body. It is specific to the drug and pharmacokinetic parameter being described.

$NFWT_{STD}$ may then be computed for a standard individual of 70 kg and 1.76 m. Allometrically scaled size based on NFWT can then be calculated from Equation 16:

$$Fsize, NFWT = \left(\frac{NFWT}{NFWT_{STD}}\right)^{3/4}. \qquad 16.$$

Although the models have empirical features, they are based on strong underlying biological mechanisms. Adult data from the literature suggests that if a person is smaller than ideal body weight then scaling dose to body weight is appropriate. When a person is larger than ideal body weight, dose should be scaled to ideal body weight or to ideal body weight plus some fraction of the difference between total weight and ideal body weight (140, 141). However, ideal body weight has no physiological basis and is derived simply in relation to actuarial predictions of life span. Renal clearance is not increased in obese adults (141) and it is unlikely that hepatic function is linearly increased with total body weight in obese people. Similar considerations apply in obese children. FFM predictions can separate the nonfat and fat components of weight. It would be reasonable to suppose that FFM alone is a good predictor of clearance because it is not a clearance organ and is unlikely to be a determinant of elimination function. On the other hand, for drugs that are lipophilic there may be a better explanation of volume of distribution by considering both FFM and a drug-specific function of fat weight.

8. CONCLUSIONS

Size is the primary covariate for pharmacokinetic parameters. Weight is an easily measured marker of size. An established scientific framework is supportive of an allometric-based model for weight with a coefficient of 0.75 for clearance and 1 for volume. Estimates of the allometric coefficient may be quite imprecise depending on the number of subjects and the distribution of weight in the sample. Consistently replicable estimates of clearance allometric coefficients that are significantly different from 0.75 have not been reported. We believe there is no evidence to reject allometric theory for predictions of drug clearance in humans. Fat is a structural feature of the body that contributes little to the metabolic rate and thus FFM might be expected to do better than total body weight when there are wide variations in fat affecting body composition.

The most obvious application of assuming the allometric theoretical model is in separating out the covarying effects of growth (weight) and maturation (age) on pharmacokinetic parameters. Clearance pathways develop in the fetus before birth. Improvements in neonatal intensive care medicine have allowed survival of neonates younger than 24 weeks PMA and with weights less than 500 g. The use of PNA as a descriptor of maturation is unsatisfactory because of the large variability in weight and gestation possible at birth; PMA is a superior marker. An asymptotic exponential function has been used to investigate clearance maturation. This asymptotic exponential model suffers because it assumes zero clearance when gestation is advanced and functioning organs capable of drug clearance are present. A sigmoid E_{max} model allows gradual maturation of clearance in early life and a "mature" clearance to be achieved at a later age. During adolescence, hormone changes, for example, may increase or decrease clearance compared with that predicted by age, but evidence is sparse in this age group. Similarly, clearance may change as a consequence of being born, although data supportive of this are lacking.

Babies and infants are young children because of the immaturity of renal and metabolic systems. Children, however, closely resemble small adults. We conclude with the proposal that, at least in terms of pharmacokinetics, the widely quoted aphorism "Children are not small adults" (e.g., 142) should be changed to "Children are small adults—babies are young children."

SUMMARY POINTS

1. There is considerable between-subject PK parameter variability within the human population. Size and age are two factors explaining a substantial part of variability across the human lifespan.
2. There is a nonlinear relationship between clearance and size. The linear per kilogram model, based on adult values, underestimates clearance and, consequently, maintenance dose in children.

3. Weight is an easily measured marker of size; fat free mass might be expected to do better than total body mass when there are wide variations in fat affecting body composition.
4. Allometry disentangles size from age, allowing a consistent approach to describing data in children and adults. An established scientific framework is supportive of an allometric-based model for weight with a coefficient of 0.75 for clearance and 1 for volume.
5. Consistently replicable estimates of clearance allometric coefficients that are significantly different from 0.75 have not been reported. We believe there is no evidence to reject allometric theory for predictions of drug clearance in humans.
6. Clearance pathways develop in the fetus before birth and PMA is a better descriptor of maturation than PNA.
7. A sigmoid E_{max} model allows gradual maturation of clearance in early life and a mature "adult" clearance to be achieved at a later age.

FUTURE ISSUES

1. Determination of in vivo, rather than in vitro, maturation of individual enzyme pathways responsible for clearance is needed.
2. The contribution of the placenta to total clearance in the fetus must be delineated.
3. Researchers should investigate the hypothesis that changes in elimination pathways are triggered by birth.
4. What is the impact of hormonal changes on clearance pathways during adolescence?
5. PBPK models need to be refined.
6. Researchers should explore pharmacodynamic differences between children and adults.

DISCLOSURE STATEMENT

Brian Anderson has received honoraria for talks and consultancies and support for travel costs to conferences from Bristol-Myer Squibb, Reckitt Benckiser, SmithKline Beecham, McNeil, and Neuren Pharmaceuticals.

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